

ORIGINAL ARTICLE

Prognosis of patients with adult T-cell leukemia/lymphoma in Japan: A nationwide hospital-based study

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Abstract

Adult T-cell leukemia/lymphoma (ATL) is a mature T-cell neoplasm and is classified into four subtypes (acute, lymphoma, chronic, and smoldering) according to the Shimoyama classification, established in 1991 through several nationwide surveys based on the clinical diversity of patients diagnosed in 1983-1987 in Japan. Thereafter, no such studies have been conducted. Recently, we conducted a nationwide hospital

Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplantation; ATL, adult T-cell leukemia/lymphoma; AZT, zidovudine; BUN, blood urea nitrogen; CCR4, CC chemokine receptor 4; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; HTLV-1, human T-cell leukemia virus type-1; IFN, interferon- α ; IQR, interquartile range; IRF4, interferon regulatory factor 4; LDH, lactate dehydrogenase; MST, median survival time; OS, overall survival; PD-L1, programmed death-ligand 1; PS, performance status; VCAP-AMP-VECP, vincristine, cyclophosphamide, doxorubicin and prednisone, followed by doxorubicin, ranimustine, and prednisone and then by vindesine, etoposide, carboplatin, and prednisone.

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Yoshitaka Imaizumi, Masako Iwanaga and Kunihiro Tsukasaki are contributed equally to this work.

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Funding information

Grants-in-Aid from the Ministry of Health, Labour and Welfare of Japan, Grant/Award Number: H23-GanRinsho-Ippan-020 and H26-GanSeisaku-Ippan-006; the Japan Agency for Medical Research and Development, Grant/Award Number: 17ck0106338h0001 and 18ck0106338s0502

survey using the method of the 1980s studies, collected baseline data on 996 ATL patients diagnosed in 2010-2011 from 126 hospitals, and reported their unique epidemiological characteristics. Here, we report the follow-up results of registered ATL patients with the goal of evaluating current prognoses and treatment modalities as of 2016-2017. Of 770 evaluable patients, 391 (50.8%) had acute-type, 192 (24.9%) had lymphoma-type, 106 (13.8%) had chronic-type, and 81 (10.5%) had smoldering-type ATL. The initial therapy regimens used for acute/lymphoma-type ATL were vincristine, cyclophosphamide, doxorubicin and prednisone, followed by doxorubicin, ranimustine, and prednisone and then by vindesine, etoposide, carboplatin, and prednisone (VCAP-AMP-VECP)-like in 38.5/41.7% and cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-like in 14.6/13.7% of patients. Allogeneic hematopoietic stem cell transplantation was used to treat 15.9/10.4% of acute/lymphoma-type ATL patients. The 4-year survival rates (the median survival time, days) for acute-, lymphoma-, unfavorable chronic-, favorable chronic-, and smoldering-type ATL were 16.8% (252), 19.6% (305), 26.6% (572), 62.1% (1937), and 59.8% (1851), respectively. The 4-year survival rates for acute- and lymphoma-type ATL improved compared with those reported in 1991, but those for chronic- and smoldering-type ATL were not. Further efforts are warranted to develop more efficient therapeutic strategies to improve the prognosis of ATL in Japan.

KEYWORDS

ATL, clinical subtypes, HTLV-1, Japanese nationwide survey, prognosis

1 | INTRODUCTION

Adult T-cell leukemia/lymphoma (ATL) is a mature, peripheral T-cell malignancy¹ caused by human T-cell leukemia virus type I (HTLV-1) infection.^{2,3} Regions of high HTLV-1 endemicity and ATL prevalence are limited to Japan, sub-Saharan Africa, South America, and central Australia.⁴ Worldwide, at least 3000 new cases of ATL are diagnosed each year.⁵ In Japan, there are one million HTLV-1 carriers,⁶ 4000 new HTLV-1 infections annually,⁷ and 1000 deaths from ATL annually.⁸

The diagnostic criteria and subtypes of ATL were first established in Japan in 1991 by the Lymphoma Study Group of Japan Clinical Oncology Group (JCOG)⁹ based on the prognoses of patients enrolled in several nationwide hospital-based surveys from 1983-1987.^{10,11} These criteria are now known as the "Shimoyama classification."

It has been over 25 years since the establishment of the criteria for ATL,⁹ and various treatment options are now available. These include "watchful waiting" for indolent ATL (smoldering- and favorable chronic-types)¹² and a variety of intensive chemotherapies followed by allogeneic hematopoietic stem cell transplantation (allo-HSCT) for aggressive ATL (acute-, lymphoma-, and unfavorable chronic-types).^{13,14} More recently, several promising new agents, including an anti-CCR4 antibody (mogamulizumab)¹⁵ and an immunomodulatory agent (lenalidomide)¹⁶ have been approved for aggressive ATL. Therefore, it was expected that the prognoses of patients with

ATL in Japan would improve compared with those reported in the 1980s-1990s.

However, the majority of previous reports from Japan have suggested that ATL patient outcomes have not improved as expected.¹⁷⁻¹⁹ As an example, a study of 1594 ATL patients diagnosed in 2000-2009¹⁹ reported that the 4-year survival of smoldering-type ATL was lower than in the 1991 report,⁹ despite an improvement of survival rates for acute/lymphoma-type ATL. However, most of the study procedures in the previously published reports differed from those of the 1991 report,⁹ particularly in collecting data from participating hospitals. Therefore, to evaluate more precisely whether the prognostic features of current patients with ATL have changed compared with those in the 1991 report,⁹ it is necessary to analyze data on recent ATL patients using similar procedures to those of the 1991 report.

We have already conducted a nationwide survey study of newly diagnosed ATL patients in 2010-2011 in all of Japan²⁰ using similar procedures to those of the 1991 report,⁹⁻¹¹ accumulated data on 996 patients from 126 hospitals, and reported a significant shift toward older age at diagnosis and an increasing proportion of lymphoma-type ATL in older patients compared with the 1991 report. However, we have not yet evaluated the outcomes of the registered patients. We therefore conducted this follow-up survey study in a nationwide setting, using a similar method to that of the 1991 report.^{10,11}

The primary purpose of this study was to evaluate the prognosis of ATL patients by clinical subtypes and by treatment modality

across Japan from the date of diagnosis in 2010-2011 until the latest follow-up or death by 2016-2017. Then, we evaluated whether the prognoses of recently diagnosed ATL patients have improved compared with those described in the 1991 Shimoyama report in Japan.⁹

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This was a retrospective, observational, multicenter, hospital-based study of ATL patients newly diagnosed in 2010-2011 at 126 participating hematological and dermatological departments across Japan. The patients had already been registered in the baseline database developed through our nationwide, multicenter, hospital-based study.²⁰ In this follow-up study, we additionally collected data on treatments and outcomes for all registered patients as of 2016-2017. The study protocol was approved by the ethics committee and institutional review board (IRB) of the National Cancer Center of Japan (approval no. 2014-235). The ethical committee waived the need for written informed consent because of the retrospective nature of the study and anonymous data collection.

The study procedures followed as much as possible those of the 1991 report,⁹ in which the diagnostic criteria for ATL were first described.⁹ First, we inquired whether the chief physician of each hospital would be able to participate in this follow-up study by sending a questionnaire to all 126 participating hospitals between April and

June of 2016. The first questionnaires were returned by 113 hospitals (89.6%); of those, 98 (85.7%) hospitals agreed to participate in this follow-up study after the approval of the study protocol by the regional IRB of each hospital. We then sent the follow-up survey to each of the 98 hospitals. The survey consisted of the following elements: (a) patient baseline information recorded in the database of the first survey²⁰; (b) final outcome status, including causes of death; (c) chemotherapy status and response status to initial regimens; (d) status of radiotherapy, anti-CCR4 antibody therapy, and allo-HSCT; (e) information on ATL subtype and on acute transformation when any therapeutic options started in indolent subtypes. A reminder letter was mailed if the survey was not returned. All data were collected by a professional clinical research support office (Ata-Life Inc, Tokyo, Japan) by the end of April 2017 and the data cleaning process was completed by the end of September 2018.

This follow-up study focused on the treatment and outcome of ATL by clinical subtype, clinical condition at diagnosis, and treatment modality, but not on prognostic parameters, through multivariate analysis. We used the centrally reviewed subtypes of ATL in our previous baseline data.²⁰ The diagnostic agreement for subtype classification between participating institutions and central review was 0.72.

2.2 | Statistical analysis

Continuous variables were summarized as medians [range or interquartile range (IQR)] and compared using Wilcoxon's rank-sum test.

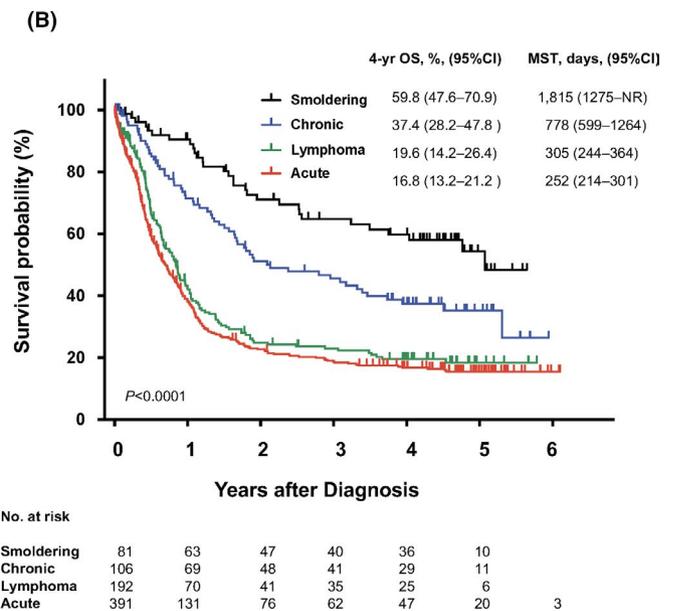
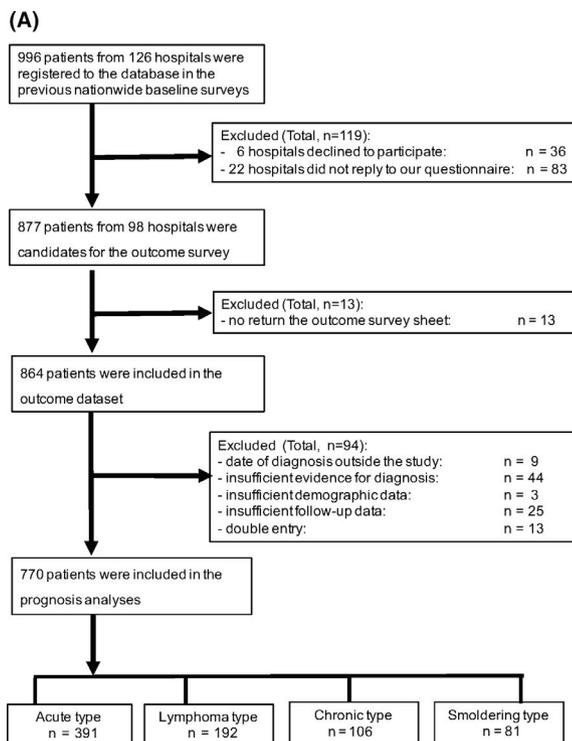


FIGURE 1 A, Study flow chart for patient inclusion/exclusion. B, Overall survival (OS) and median survival time (MST) by adult T-cell leukemia/lymphoma (ATL) subtype

Continuous variables were also stratified into groups as necessary. Differences in the frequencies of categorical variables were compared using the chi-square test or Fisher's exact test. Follow-up duration was calculated from the diagnosis date to the date of death or the last follow-up at participating hospitals. A cumulative 4-year overall survival (OS) rate and a median survival time (MST) were estimated using the Kaplan-Meier method, and curve comparison was performed using both the log-rank test and the generalized Wilcoxon test. MST was defined as the time at which the cumulative survival probability was 50%. Graphical and statistical analyses were performed using GraphPad Prism 7.0 (GraphPad Software) and JMP Pro 13 (SAS Institute). Two-sided *P*-values < 0.05 were considered statistically significant.

3 | RESULTS

3.1 | Characteristics of patients

Figure 1A shows inclusion/exclusion of patients according to the STROBE guidelines.²¹ Among 996 patients registered in the baseline study,²⁰ 119 were excluded due to lack of participation information

from hospitals. The remaining 877 patients (88.1%) from 98 hospitals were initially included. However, four hospitals that had previously registered 13 patients did not return outcome information, and thus we included 864 patients in the outcome dataset. Of 864 patients, 94 were excluded during the central review process. Finally, 770 patients were included in the prognosis analysis. Of 770 patients, 391 (50.8%) had acute-type, 192 (24.9%) had lymphoma-type, 106 (13.8%) had chronic-type, and 81 (10.5%) had smoldering-type ATL based on previous central review.²⁰ The demographic and clinical characteristics at diagnosis of the 770 patients are summarized by subtype in Table 1.

3.2 | Treatment regimens

Among 391 patients with acute-type ATL, 343 (87.7%) received chemotherapies (Table 2). Of these patients, 161 (46.9%) received VCAP-AMP-VECP-like regimens,²² 132 (38.5%) received CHOP-like regimens, and the remainder received other regimens (Table S1). The choice of chemotherapy regimen for acute-type ATL patients differed significantly by age and B-symptom status, but not by Eastern Cooperative Oncology Group performance status (PS) nor

TABLE 1 Clinical characteristic of patients with adult T-cell leukemia/lymphoma (ATL) at diagnosis by subtypes

Characteristic	Summary unit	Total No. evaluated	ATL subtype according to Shimoyama's classification			
			Acute (n = 391)	Lymphoma (n = 192)	Chronic (n = 106)	Smoldering (n = 81)
Male Sex	n (%)	770	211 (54.0)	113 (58.9)	43 (40.6)	44 (54.3)
Age at diagnosis	Median (range) y	770	68 (34-94)	70 (37-91)	65 (36-85)	68 (40-89)
WBC count	Median (range) x10 ⁹ /L	770	12.3 (2.3-257)	6.2 (1.1-34.9)	14.0 (7.6-234.9)	6.4 (1.5-11.4)
Abnormal lymphocyte	% of WBC	767	19 (0-99.5)	0-1	37 (0-95)	6 (0-34)
Serum albumin	Median (range) g/dL	757	3.5 (0-5)	3.7 (1.6-4.8)	4 (0-5)	4.2 (0-4.9)
BUN	Median (range) mg/dL	767	16.4 (4.8-170)	15.1 (4.7-57.5)	13.5 (0-26.7)	15.5 (7-45.2)
Creatinine	Median (range) mg/dL	769	0.8 (0.3-9.4)	0.77 (0.29-10.4)	0.7 (0.4-1.6)	0.8 (0.3-2.6)
CRP	Median (range) mg/dL	765	0.9 (0-34.9)	0.9 (0-29)	0.2 (0-17.6)	0.1 (0-5.1)
sIL-2R	Median (range) U/mL	720	23 900 (316-41.7 × 10 ⁶)	10 661 (290-4 × 10 ⁵)	6581 (200-66.6 × 10 ³)	1076 (8.7-52.8 × 10 ³)
LDH	Median (range) IU/L	769	583 (132-13 990)	398 (150-16 900)	257 (145-467)	216 (125-341)
LDH > ULN	%	770	87.7	87.0	56.6	38.3
Hypercalcemia present (>11)	%	744	30.3	14.4	0	0
Ann Arbor stage, I-II	%	722	0.5	24.0	0	0
ECOG PS (0-1)	%	750	53.5	65.1	88.4	89.7
B symptoms present	%	731	31.1	26.1	10.9	4.1

Abbreviations: BUN, blood urea nitrogen; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PS, performance status; sIL-2R, soluble interleukin-2 receptor; ULN, upper limit of normal; WBC, white blood cells.

TABLE 2 Diversity in treatment options and chemotherapy response for acute or lymphoma type of adult T-cell leukemia/lymphoma (ATL)

Subtype and condition	Systematic chemotherapy received, n	First systematic chemotherapy regimens n (% of row)			Chemotherapy responses n (% of row)							Allo-HSCT received n (% of row)	P
		VCAP-AMP-VECP regimen or the like	CHOP regimen or the like	Others ^a	CR	PR	SD (NC)	PD	Unknown	P			
Acute type													
Chemotherapy received, all	343	161 (46.9)	132 (38.5)	50 (14.6)	49 (14.3)	169 (49.3)	39 (11.4)	67 (19.5)	19 (5.5)			62	
Age at diagnosis													
<70 y	198	122 (61.6)	60 (30.3)	16 (8.1)	<.0001	40 (20.5)	90 (46.2)	24 (12.3)	32 (16.4)	9 (4.6)	.0024	61 (30.8)	<.0001
≥70 y	145	39 (26.9)	72 (49.7)	34 (23.4)	9 (6.3)	79 (55.6)	15 (10.6)	35 (24.7)	4 (2.8)			1 (0.7)	
ECOG PS													
PS 0-1	188	96 (51.0)	67 (35.6)	25 (13.3)	.27	36 (19.4)	90 (48.4)	17 (9.1)	39 (20.4)	5 (2.7)	.05	50 (26.6)	<.0001
PS 2-4	149	63 (42.3)	61 (40.9)	25 (16.8)		13 (9.0)	75 (51.7)	22 (15.2)	28 (19.3)	7 (4.8)		12 (8.1)	
Unknown	6												
Hypercalcemia													
Absent	234	116 (49.6)	89 (38.0)	29 (12.4)	.19	38 (16.5)	109 (47.4)	29 (12.6)	45 (19.6)	9 (3.9)	.49	49 (20.9)	.14
Present	100	41 (41.0)	40 (40.0)	19 (19.0)		10 (10.2)	55 (56.1)	10 (10.2)	20 (20.4)	3 (3.1)		12 (10.4)	
Unknown	9												
B symptoms													
Absent	225	113 (50.2)	74 (32.9)	38 (16.9)	.009	32 (14.2)	113 (50.2)	26 (11.6)	40 (17.8)	14 (6.2)	.4	43 (19.4)	.65
Present	103	40 (38.8)	52 (50.5)	11 (10.7)		14 (13.6)	50 (48.5)	13 (12.6)	23 (22.3)	3 (2.9)		17 (16.7)	
Unknown	15												
Lymphoma type													
Chemotherapy received, all	175	78 (44.6)	73 (41.7)	24 (13.7)	39 (22.3)	79 (45.1)	26 (14.9)	26 (14.9)	5 (2.8)			20	
Age at diagnosis													
<70 y	85	49 (57.6)	32 (37.7)	4 (4.7)	.0002	27 (31.7)	35 (41.2)	5 (5.9)	15 (17.7)	3 (3.5)	.001	20 (23.5)	<.0001
≥70 y	90	29 (32.2)	41 (45.6)	20 (22.2)		12 (13.5)	44 (49.4)	21 (23.6)	11 (12.4)	1 (1.1)		0	
ECOG PS													
PS 0-1	112	51 (45.5)	47 (42.0)	14 (12.5)		31 (27.7)	50 (44.6)	15 (13.4)	13 (11.6)	3 (2.7)	.12	17 (15.2)	.12
PS 2-4	57	23 (40.4)	24 (42.1)	10 (17.5)	.63	7 (12.5)	26 (46.4)	9 (16.1)	13 (23.1)	1 (1.8)		3 (5.3)	
Unknown	6												

(Continues)

TABLE 2 (Continued)

Subtype and condition	First systematic chemotherapy regimens n (% of row)			Chemotherapy responses n (% of row)									
	Systematic chemotherapy received, n	VCAP-AMP-VECP regimen or the like	CHOP regimen or the like	Others ^a	P	CR	PR	SD (NC)	PD	Unknown	P	Allo-HSCT received n (% of row)	P
Hypercalcemia													
Absent	146	68 (46.6)	57 (39.0)	21 (14.4)	.47	32 (22.1)	67 (46.2)	21 (14.5)	23 (15.9)	2 (1.4)	.27	15 (10.3)	.65
Present	25	9 (36.0)	13 (52.0)	3 (12.0)		6 (24.0)	29 (36.0)	5 (20.0)	3 (12.0)	2 (8.0)		4 (16.0)	
Unknown	4												
B symptoms													
Absent	127	59 (46.4)	50 (39.4)	18 (14.2)	.27	27 (21.3)	62 (48.8)	21 (16.5)	13 (10.2)	4 (3.1)	.04	15 (10.3)	.2
Present	41	14 (34.1)	22 (53.7)	5 (12.2)		9 (22.0)	16 (39.0)	3 (7.3)	12 (29.3)	1 (2.4)		4 (9.8)	
Unknown	7												

Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplantation; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; ECOG, Eastern Cooperative Oncology Group; NC, no change; PD, progressive disease; PR, partial response; PS, performance status; SD, stable disease; VCAP-AMP-VECP, vincristine, cyclophosphamide, doxorubicin and prednisone, followed by doxorubicin, ranimustine, and prednisone and then by vindesine, etoposide, carboplatin, and prednisone.

^aOther miscellaneous regimens are summarized in Table S1.

by hypercalcemia status. For patients aged < 70 years, VCAP-AMP-VECP-like regimens were the most common (61.6%) followed by CHOP-like regimens, whereas for those aged ≥ 70 years, CHOP-like regimens were the most common (49.7%). Allo-HSCT was administered in 62 (15.9%) acute-type ATL patients; the majority were those aged < 70 years (n = 61), those with good PS, and those without hypercalcemia at diagnosis. The chemotherapy regimens were decided by the attending hematologists or dermatologists in each hospital, and information on the reasons for the choice of chemotherapy regimen was not collected in this study.

Among 192 patients with lymphoma-type ATL, 175 (91.1%) received chemotherapies, 11 (5.7%) did not receive any chemotherapy, and the remainder had unknown status (3.1%). Of those who received any chemotherapies (Table 2), 78 (44.6%) received VCAP-AMP-VECP-like regimens, 73 (41.7%) received CHOP-like regimens, and the remainder received other regimens (Table S1). The chemotherapy regimens for lymphoma-type ATL patients differed significantly by age (Table 2), but not by PS, hypercalcemia status, or B symptom status. Allo-HSCT was administered in 20 (10.4%) lymphoma-type ATL patients (only in those aged < 70 years); the majority were patients with good PS and without hypercalcemia.

Among 106 patients with chronic-type ATL, 71 (67.0%) had unfavorable chronic-type ATL, 33 (31.1%) had favorable chronic-type ATL (Table 3), and the information on the poor prognostic factors was not available for the remaining patients. Among patients with unfavorable chronic-type ATL, 54 (76.0%) received chemotherapies with a median interval from diagnosis to initiation of chemotherapy of 21 days (IQR, 7-118 days) (Table 3). The chemotherapy regimens received were VCAP-AMP-VECP-like regimens in 22 patients (40.8%), CHOP-like regimens in 12 patients (22.2%), and other regimens in 20 patients (37.0%) (Table S1). Thirteen (18.3%) patients with unfavorable chronic-type ATL received allo-HSCT following chemotherapy, 41 (57.7%) received chemotherapy alone, 16 (22.5%) received no chemotherapy, and one had insufficient data. Among patients with favorable chronic-type ATL, 20 (60.6%) received chemotherapy (Table 3) due to progression to unfavorable chronic-type ATL (n = 9) or acute transformation (n = 11). The median interval from diagnosis to initiation of chemotherapy was 566 days, significantly longer compared with patients with unfavorable chronic-type ATL (P = 0.002). The chemotherapy regimens used for favorable chronic-type ATL were VCAP-AMP-VECP-like regimens in 12 patients (60%) and CHOP-like regimens in five patients (25%) (Table 3). Patients aged < 70 years received VCAP-AMP-VECP-like regimens more often than those aged ≥ 70 years (P = .049). Eight (24.2%) patients with favorable chronic-type ATL received allo-HSCT following chemotherapy, 11 (33.3%) were treated with chemotherapy alone, one received chemotherapy but had no available data on allo-HSCT, 12 (36.4%) received no chemotherapy, and one had no available data on chemotherapy.

Among 81 patients with smoldering-type ATL, 43 (53.8%) had skin lesions and received a variety of topical treatments (data not shown). During follow-up, 30 of 81 patients (37%) received chemotherapies due

TABLE 3 Diversity in treatment options for chronic or smoldering subtypes of adult T-cell leukemia/lymphoma (ATL)

Subtype and condition	Systematic chemotherapy received, n	Days from diagnosis to chemotherapy median (ranges)	P	First systematic chemotherapy regimens, n (% of row)				Chemotherapy responses, n (% of row)					allo-HSCT received, n
				VCAP-AMP-VEC P or the like	CHOP or the like	Others ^a	P*Fischer	CR	PR	SD (NC)	PD	Unknown	
Unfavorable chronic type													
N. received	54	21 (0-1862)		22 (40.8)	12 (22.2)	20 (37.0)	-	8 (14.8)	27 (50.0)	6 (11.1)	13 (24.1)		13
Age at diagnosis													
<70 y	33	19 (0-1862)	0.9	19 (57.6)	6 (18.2)	8 (24.2)	.45	4 (12.2)	18 (54.5)	4 (12.2)	7 (21.2)		13
≥70 y	21	22 (1-757)		3 (14.3)	6 (28.6)	12 (57.1)		5 (19.1)	9 (42.9)	2 (9.5)	6 (28.6)		0
ECOG PS at diagnosis													
PS 0,1	47	19 (0-757)	0.7	21 (44.7)	11 (23.4)	15 (31.9)	.07	7 (14.9)	24 (51.1)	5 (10.6)	11 (23.4)		13
PS 2-4	5	18 (2-89)		0	1 (20.0)	4 (80.0)		1 (20.0)	2 (40.0)	1 (20.0)	1 (20.0)		0
Unknown													
Skin lesion													
Absent	31	15.5 (0-1862)	0.99	13 (41.9)	6 (19.4)	12 (38.7)	.78	4 (12.9)	15 (48.4)	3 (9.7)	9 (29.0)		5
Present	22	26.5 (1-477)		9 (40.9)	6 (27.3)	7 (31.8)		3 (13.6)	12 (54.6)	3 (13.6)	4 (18.2)		7
Unknown													
Favorable chronic type													
N. received	20	566 (2-1460)		12 (60.0)	5 (25.0)	3 (15.0)	-	3 (15.0)	9 (45.0)	6 (30.0)	1 (5.0)		8
Age at diagnosis													
<70 y	17	566 (2-1460)	0.52	12 (70.6)	3 (17.7)	2 (11.7)	.049	3 (17.7)	8 (47.1)	4 (23.5)	1 (5.9)		8
≥70 y	3	301 (6-596)		0	2 (66.7)	1 (33.3)		0	1 (33.3)	2 (66.7)	0		0
ECOG PS at diagnosis													
PS 0,1	20	566 (2-1460)	-	12 (60.0)	5 (25.0)	3 (15.0)	-	3 (15.0)	9 (45.0)	6 (30.0)	1 (5.0)		8
PS 2-4	0							0	0	0	0		
Skin lesion													
Absent	12	499 (2-1460)	0.14	8 (66.7)	3 (25.0)	1 (8.3)	.81	3 (25.0)	7 (58.3)	1 (8.3)	1 (8.3)		2
Present	8	726 (86-1098)		4 (50.0)	2 (25.0)	2 (25.0)		0	2 (25.0)	5 (62.5)	0		6
Smoldering type													
N. received	30	232 (23-1344)		9 (30.0)	8 (26.7)	13 (43.3)	-	3 (10.0)	12 (40.0)	6 (20.0)	6 (20.0)		6
Age at diagnosis													
<70 y	22	228 (23-1344)	0.77	9 (40.9)	7 (31.8)	6 (27.3)	.01	3 (13.6)	11 (50.0)	2 (9.1)	4 (18.2)		6
≥70 y	8	236 (63-1186)		0	1 (12.5)	7 (87.5)		0	1 (12.5)	4 (50.0)	2 (25.0)		0

(Continues)

TABLE 3 (Continued)

Subtype and condition	Systematic chemotherapy received, n	Days from diagnosis to chemotherapy, median (ranges)	First systematic chemotherapy regimens, n (% of row)			Chemotherapy responses, n (% of row)							allo-HSCT received, n			
			VCAP-AMP-VECP or the like	CHOP or the like	Others ^a	P	VCAP-AMP-VECP or the like	CHOP or the like	Others ^a	P*Fischer	CR	PR		SD (NC)	PD	Unknown
ECOG PS at diagnosis																
PS 0-1	28	236 (23-1344)	-	9 (32.1)	8 (28.6)	11 (39.3)	-	3 (10.7)	12 (42.9)	6 (21.4)	4 (14.3)	3	-	-	-	6
PS 2-4	1	101		0	0	1		0	0	0	1					0
Unknown	1															
Skin lesion																
Absent	8	417 (64-1212)	0.39	1 (12.5)	1 (12.5)	6 (75.0)	.14	1 (12.5)	2 (25.0)	2 (25.0)	2 (25.0)			.8		1
Present	21	228 (23-1344)		8 (38.1)	7 (33.3)	6 (28.6)		2 (9.52)	10 (47.6)	4 (19.1)	3 (14.3)	2				5
Unknown	1															

Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplantation; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; ECOG, Eastern Cooperative Oncology Group; NC, no change; ND, not done; P*Fischer, Fisher's exact test; P, P-value; PD, progressive disease; PR, partial response; PS, performance status; SD, stable disease; VCAP-AMP-VECP, vincristine, cyclophosphamide, doxorubicin and prednisone, followed by doxorubicin, ranimustine, and prednisone and then by vindesine, etoposide, carboplatin, and prednisone.

^aOther miscellaneous regimens are summarized in Table S1.

TABLE 4 Prognosis variation of adult T-cell leukemia/lymphoma (ATL) by subtype

Items related to prognosis	Acute (n = 391)	Lymphoma (n = 192)	Among chronic subtype		Among smoldering subtype			
			Chronic (n = 106)	Unfavorable (n = 71)	Favorable (n = 33)	Smoldering (n = 81)	Skin lesion positive (n = 43)	Skin lesion negative (n = 37)
Follow-up duration for all, median (IQR), d	210 (101-468)	252 (131-619)	631 (217-1467)	425 (183-1467)	1438 (612-1607)	968 (386-1693)	662 (394-1701)	1494 (370-1692)
Follow-up duration only for alive patients, median (IQR), d	1354 (110-1784)	1440 (106-1688)	1491 (535-1761)	1543 (267-1878)	1481 (1060-1690)	1561 (419-1744)	1379 (293-1731)	1594 (1202-1757)
No. of deaths (proportion of each total)	297 (76.0%)	139 (72.4%)	61 (57.5%)	47 (66.2%)	13 (39.4%)	30 (37.0%)	18 (41.9%)	11 (29.7%)
MST (95%CI), d	252 (214-301)	305 (244-364)	778 (599-1264)	572 (339-690)	1937 (1137-1937)	1851 (1275-NR)	1739 (594-NR)	NR
4-year survival rate (95%CI), %	16.8 (13.2-21.2)	19.6 (14.2-26.4)	37.4 (28.2-47.8)	26.6 (17.1-38.9)	62.1 (43.4-77.7)	59.8 (47.6-70.9)	54.3 (37.6-70.0)	68.5 (50.6-82.1)

Abbreviations: CI, confidence interval; IQR, interquartile range; MST, median survival time; NR, not reached.

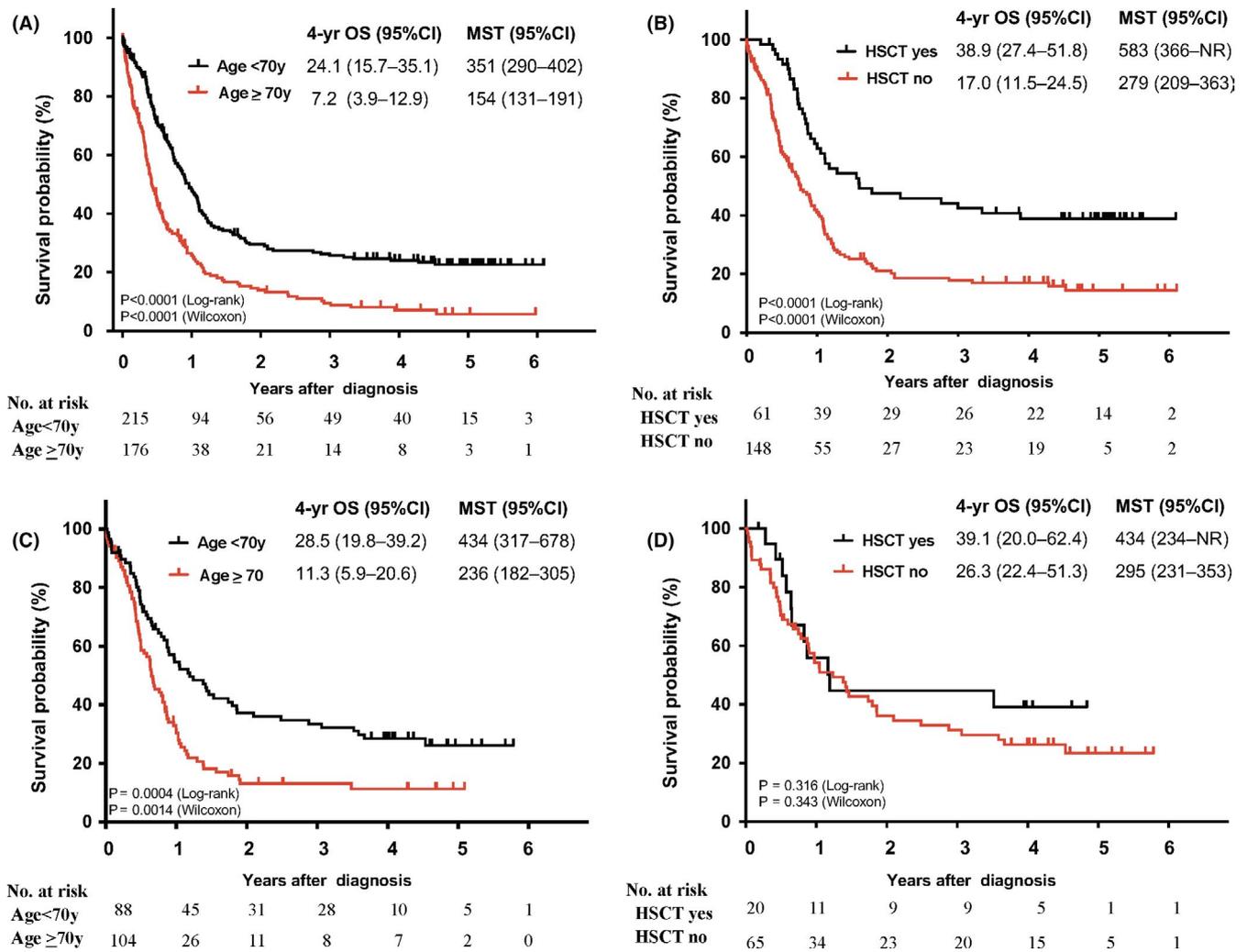


FIGURE 2 Survival analysis of acute and lymphoma adult T-cell leukemia/lymphoma (ATL) subtypes. A, Overall survival (OS) in acute ATL by age stratum at diagnosis. B, OS in acute ATL by allogeneic hematopoietic stem cell transplantation (allo-HSCT) status among patients aged < 70 y. C, OS in lymphoma ATL by age stratum at diagnosis. D, OS in lymphoma ATL by allo-HSCT status among patients aged < 70 y. Abbreviations: CI, confidence interval; MST, median survival time; NR, not reached

to acute crisis (n = 26) and worsened skin lesions (n = 4) (Table 3). The chemotherapy regimens used for smoldering-type ATL were VCAP-AMP-VECP-like regimens in nine patients (30.0%) and CHOP-like regimens in eight patients (26.7%) (Table 3). Patients aged < 70 years were more commonly treated with VCAP-AMP-VECP-like or CHOP-like regimens, whereas those aged ≥ 70 years were more commonly treated with other regimens (Table S1) (P = .01). Among patients treated with any chemotherapy, six (7.4%) received allo-HSCT following chemotherapy; all were < 70 years old at diagnosis with good PS, and five were positive for skin lesions (Table 3). Twenty-four patients (29.6%) were treated with chemotherapy alone, and the remaining 51 (63.0%) received no chemotherapy.

3.3 | Chemotherapy responses

Responses to initial chemotherapy for patients with acute/lymphoma-type ATL are summarized in Table 2. Of 343 patients with

acute-type ATL receiving any chemotherapy, 49 (14.3%) achieved complete remission (CR) and 169 (49.3%) achieved partial remission (PR). Of 175 lymphoma-type ATL patients treated with any chemotherapy, 39 (22.3%) and 79 (45.1%) achieved CR and PR, respectively. The CR/PR rates for acute/lymphoma-type ATL were significantly lower in patients aged ≥ 70 years compared with those aged < 70 years. Moreover, CR/PR rates were significantly lower in patients with advanced PS for acute-type ATL and in those with B symptoms for lymphoma-type ATL. Patients treated with VCAP-AMP-VECP-like regimens had significantly better response than those treated with CHOP-like regimens in acute-type ATL, and there was no significant difference in response between those treated with VCAP-AMP-VECP-like regimens and those treated with CHOP-like regimens in lymphoma-type ATL (Table S4).

Responses to initial chemotherapy among patients with chronic/smoldering-type ATL are summarized in Table 3. Of 54 patients with unfavorable chronic-type ATL treated with

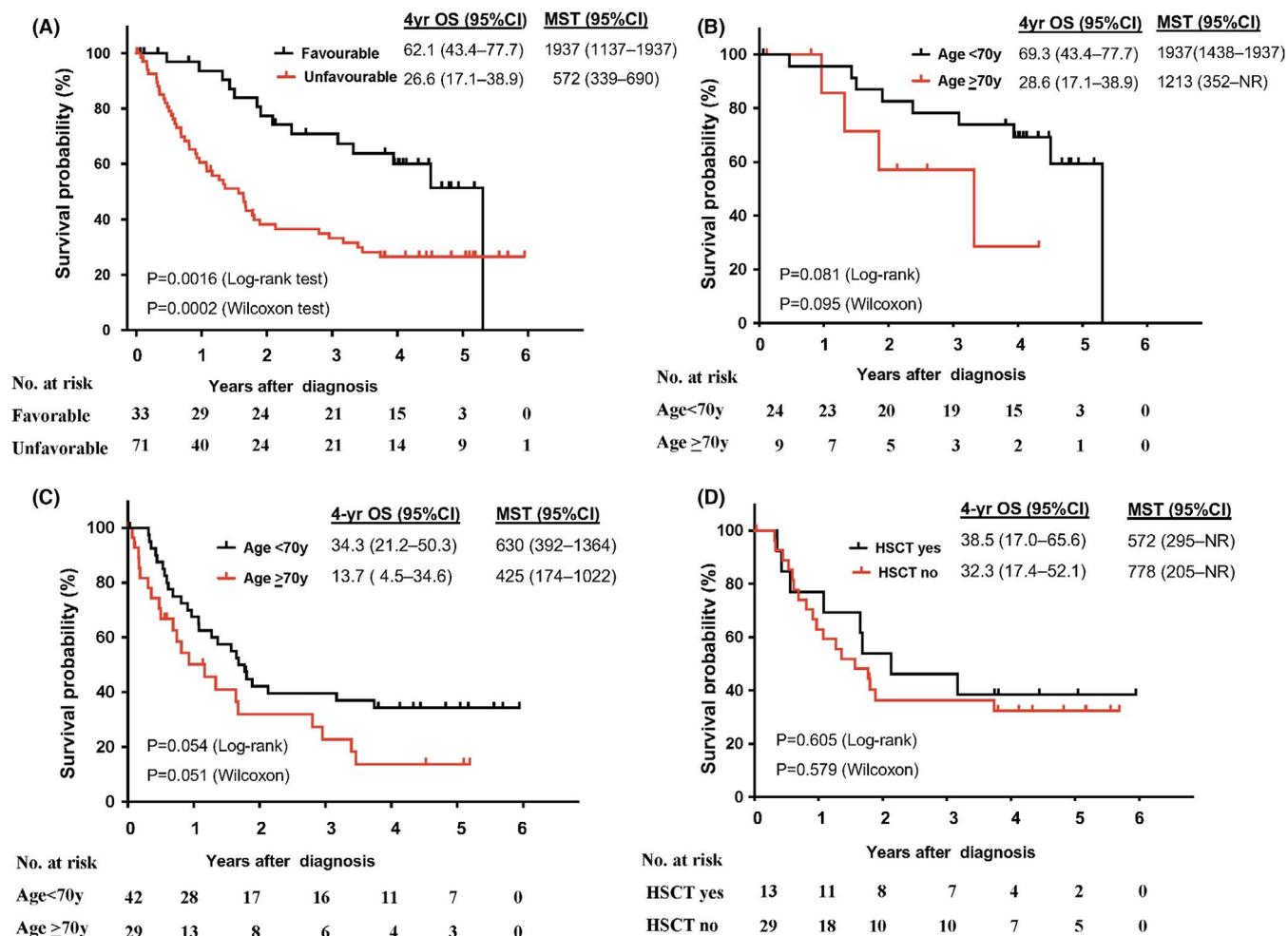


FIGURE 3 Survival analysis of chronic adult T-cell leukemia/lymphoma (ATL) subtype. A, Overall survival (OS) in chronic ATL according to favorable and unfavorable subtype. B, OS in favorable chronic ATL by age. C, OS in unfavorable chronic ATL by age. D, OS in unfavorable chronic ATL by allogeneic hematopoietic stem cell transplantation (allo-HSCT) in patients aged < 70 y. Abbreviations: CI, confidence interval; MST, median survival time; NR, not reached

any chemotherapy, 8 (14.8%) achieved CR and 27 (50.0%) achieved PR. The CR/PR rates for patients with unfavorable chronic-type ATL did not differ significantly by age, PS, or skin lesion status. Of 20 patients with favorable chronic-type ATL treated with any chemotherapy, 3 (15.0%) achieved CR and 9 (45.0%) achieved PR. The CR/PR rates did not differ significantly by age but were significantly lower in patients with skin lesions than in those without ($P = .024$). Of 30 patients with smoldering-type ATL treated with any chemotherapy, 15 (50%) achieved CR/PR, but six (20%) progressed. The CR/PR rates tended to be lower in patients aged ≥ 70 years than in those aged < 70 years ($P = .06$) but did not differ significantly by skin lesion positivity.

In summary, the CR and CR/PR rates were lowest in patients with smoldering-type ATL, intermediate in patients with acute- and favorable/unfavorable chronic-type ATL, and highest in patients with lymphoma-type ATL. However, the sample sizes were small, and the chemotherapy regimens and periods from diagnosis to initiation of chemotherapy were more diverse in patients with indolent ATL compared with aggressive ATL.

3.4 | Prognoses

At the time of last observation, 243 (31.6%) of 770 patients were alive and 527 (68.4%) had died. The median follow-up time for living patients was 1464 days (IQR, 176–883.8 days). The 4-year OS for all patients was 24.8% (95% confidence interval, 21.6–28.2%) with a MST of 355 days (IQR, 151–1438 days). The number of deaths and follow-up duration by subtype are summarized in Table 4. The 4-year OS and MST were lowest in acute-type ATL, followed by lymphoma-, chronic-, and smoldering-type ATL (Figure 1B and Table 4). The 4-year OS and MST were significantly lower for unfavorable than for favorable chronic-type ATL (Table 4, Figure 3A). Only 36 patients with acute/lymphoma-type ATL received the new agent, mogamulizumab,¹⁵ after its approval in Japan. The 3-year OS and MST in patients treated with mogamulizumab were 9% and 4.8 months, respectively (figure not shown).

The 4-year OS and MST were higher for patients aged < 70 years than for those aged ≥ 70 years with acute- (Figure 2A), lymphoma- (Figure 2C), favorable chronic- (Figure 3B), and unfavorable chronic-type (Figure 3C), but not with smoldering-type ATL (data not shown). In patients aged < 70 years, the 4-year OS of acute-type ATL

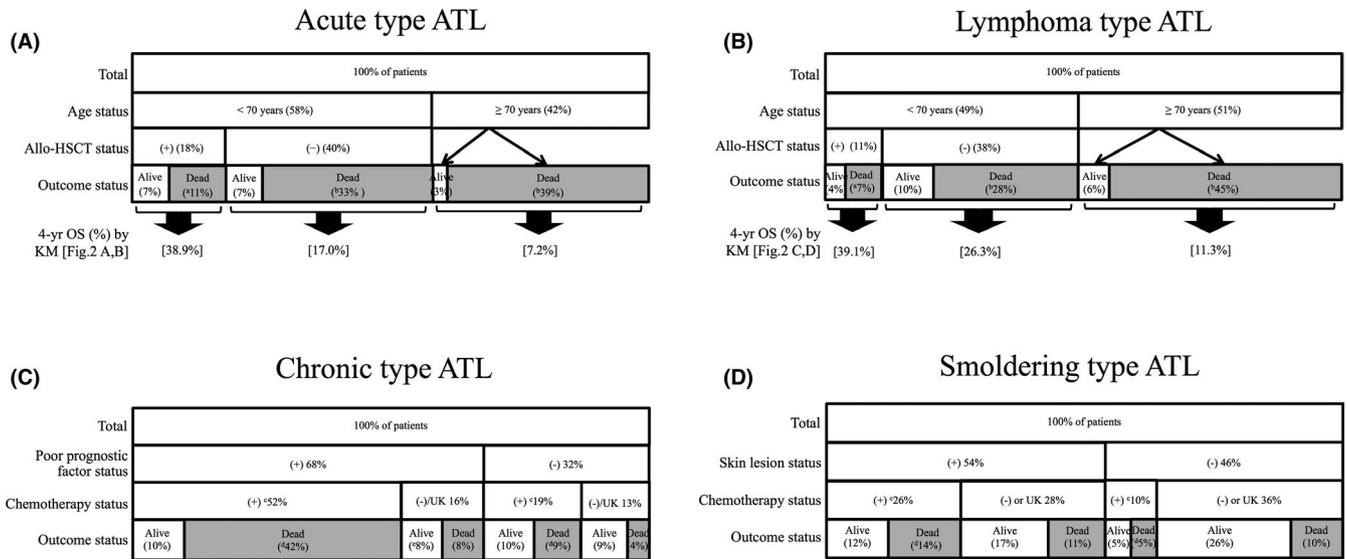


FIGURE 4 Summary of outcomes of adult T-cell leukemia/lymphoma (ATL) patients based on 4-year overall survival (OS) in Japan by subtype: acute-type (A), lymphoma-type (B), chronic-type (C), and smoldering-type (D). The percentage in each box represents the estimated proportion of patients. Results based on the outcomes of patients who received any chemotherapy are shown for acute- and lymphoma-type ATL. ^aDied despite allogeneic hematopoietic stem cell transplantation (allo-HSCT) (only patients aged < 70 y). ^bDied despite chemotherapy without allo-HSCT. ^cReceived chemotherapy during observation period. ^dDied despite chemotherapy. ^eAlive without chemotherapy in patients with unfavorable chronic-type ATL. Abbreviations: Rate at 4-y, survival rate at 4-y follow-up; UK, unknown

was significantly higher for those who received allo-HSCT (38.9%) compared with those who did not (17.0%) (Figure 2B). This was not the case for lymphoma-type ATL, although the OS tended to be higher in patients who received allo-HSCT (39.1%) than in those who did not (26.3%) (Figure 2D). The survival of patients aged < 70 without allo-HSCT was significantly higher than that of those aged ≥ 70, both in acute-type ATL ($P = .001$ by log-rank test) and in lymphoma-type ATL ($P = .0029$ by log-rank test). For patients with unfavorable chronic-type ATL aged < 70 years, the 4-year OS did not differ significantly in those who received and in those who did not receive allo-HSCT (Figure 3D). Among patients with smoldering-type ATL, there was no significant difference in 4-year OS between those with skin involvement and those without, although the survival tended to be worse in those with skin involvement (Figure S1).

Finally, we summarized the clinical outcomes of patients by ATL subtype based on the 4-year OS (Figure 4). The proportion (percentage of total) is shown for each column; by age status, by allo-HSCT status, and by outcome status in acute- and lymphoma-types; by poor prognostic factor status, by chemotherapy status, and by outcome status in chronic-type; by skin lesion status, by chemotherapy status, and by outcome status in smoldering-type. The 4-year OS is also shown for patients aged < 70 treated with or without allo-HSCT and for those aged ≥ 70 in acute- and lymphoma-types. Among all patients with acute- and lymphoma-type ATL, allo-HSCT was applied for 18% and 11%, with a 4-year OS of 7% and 4%, respectively (Figure 4A,B), and allo-HSCT was not applied for 82% and 89%, with a 4-year OS of 10% and 16%, respectively (Figure 4A,B). Among all patients with chronic-type ATL, the 4-year OS of those who received chemotherapy and those who did not was 10% and 8%, respectively, in unfavorable chronic-type ATL, and 10% and 9%, respectively, in favorable chronic-type

ATL (Figure 4C). Among all patients with smoldering-type ATL, the 4-year OS of those who received chemotherapy and those who did not was 12% and 18%, respectively, in those with skin lesions, and 5% and 26%, respectively, in those without skin lesions (Figure 4D).

3.5 | Causes of death

Among 527 patients who died, 414 (78.6%) died from ATL, 53 (10.0%) from infection, 11 (2.1%) from malignant diseases other than ATL, and the rest from other causes (Table S2). For patients with acute-, lymphoma-, and chronic-type ATL, the second most common cause of death was infection. However, for patients with smoldering-type ATL, the second most common cause of death was non-ATL malignancy (accounting for 20% of deaths).

4 | DISCUSSION

This report provides a comprehensive clinical picture of ATL patients in 2010-2011 in Japan. Our main findings are that (a) the 4-year OS for acute/lymphoma-type ATL has improved compared with that in the 1991 report⁹ despite an increasing number of older patients,²⁰ but (b) the 4-year OS of smoldering/chronic-type ATL has apparently not improved. In Table 5, we summarize the outcomes of ATL patients in Japan by subtype and by diagnosis year based on the 1991 report,⁹ the 2015 report,¹⁹ and the present report. The difference in the study design between the 2015 report and the present study is also summarized in Table S3. Although it is not possible to directly compare these studies with one another, our study provides

TABLE 5 Summary of the prognosis of adult T-cell leukemia/lymphoma (ATL) in literature and the present study

	Shimoyama report	Katsuya report	The present study
Year of published (reference No.)	1991 ¹⁴	2015 ²³	2019
Total			
Year of diagnosis	1983-1987	2000-2009	2010-2011
Year of the last follow-up	1990	NA	2016
No. evaluated	818	1594	770
Age at diagnosis, median or mean (ranges), y	57.1 (24-92)	61-63 (NA)	68 (34-94)
No. dead (% of evaluated)	565 (69.1)	1128 (70.8)	527 (68.4)
Acute			
No. evaluated	465	895	391
MST, mo	6.2	8.3	8.3
4-y survival rate (%)	5.0	11.4	16.8
Lymphoma			
No. evaluated	156	355	192
MST, mo	10.2	10.6	10.0
4-y survival rate (%)	5.7	16.2	19.6
Chronic, all			
No. evaluated	152	187	106
MST, mo	24.3	31.5	25.5
4-y survival rate (%)	26.9	35.6	37.4
Unfavorable chronic			
No. evaluated	NA	15	71
MST, mo	NA	NR	18.8
4-y survival rate (%)	NA	29.0	26.6
Favorable chronic			
No. evaluated	NA	172	33
MST, mo	NA	NR	63.5
4-y survival rate (%)	NA	60.0	62.1
Smoldering			
No. evaluated	45	157	81
MST, mo	NR	55.0	60.7
4-y survival rate (%)	62.8	51.9	59.8

Abbreviations: MST, median survival time; NA, not available; NR, not reached.

important information on the current status of patients with ATL in clinical practice in Japan.

Regarding the chemotherapy regimens used to treat patients with acute/lymphoma-type ATL, VCAP-AMP-VECP-like regimens (60%) were most common (Table 2). This is primarily because VCAP-AMP-VECP is considered a standard therapy for aggressive ATL in patients aged < 70 years in current Japan based on

the results of a phase III trial.²² The most common regimens differed from those in the 1991 report^{9,23} and the 2015 report¹⁹; in both of these previous reports, CHOP-like regimens were most common. Differences in chemotherapy regimens might be related to improvements over time in the 4-year OS of acute/lymphoma-type ATL in Japan. However, among older patients with acute/lymphoma-type ATL, the proportion who received VCAP-AMP-VECP-like regimens was low, and both the CR/PR rate and OS were lower than in younger patients (Table 2). For such elderly patients, other chemotherapies as well as mogamulizumab,¹⁵ lenalidomide,¹⁶ and other promising agents²⁴⁻²⁶ should be evaluated.

The application of allo-HSCT may also have contributed to the improved 4-year OS of acute/lymphoma-type ATL compared with the 1991 report, as recommended for consideration in a recent consensus report.²⁷ However, we found that allo-HSCT was applied in only 18% and 13% of acute- and lymphoma-type ATL patients, respectively (Figure 4). About 20% of patients aged < 70 years with acute/lymphoma-type ATL were still alive 4 years after diagnosis without allo-HSCT (Figure 4A,B). By contrast with acute-type ATL patients, improved survival for patients receiving allo-HSCT was not significant in lymphoma/unfavorable chronic-type ATL (Figures 2B, 2D, 3D, and Table 5). These findings suggest the possibility of further treatment stratification in these subtypes, although the sample size was small and the follow-up period was not long enough in this study.

Prognoses have not improved for indolent ATL in this study. One reason might be the absence of strategies to prevent progression to aggressive ATL with patients under "watchful waiting" until disease progression. Further efforts to identify early markers for progression are needed for patients with indolent ATL. Genomic abnormalities associated with poor prognosis of indolent ATL, such as interferon regulatory factor 4 (*IRF4*) mutations and programmed death-ligand 1 (*PD-L1*) amplification,²⁸ are expected to be explored as new predictive biomarkers for early intervention. Recently, a combination of interferon alpha and azidothymidine (IFN/AZT) has shown promising effectiveness for indolent ATL in Western countries, although the evidence level was not sufficient.²⁹ In Japan, a phase III study of watchful waiting versus IFN/AZT for symptomatic indolent ATL is underway (JCOG1111C).¹⁸ Deaths from comorbid diseases might be another reason for the disappointing outcome (Table S2), as deaths from infection and malignancies other than ATL were frequent in patients with chronic/smoldering-type ATL in this study.

The limitations of this study were that (a) data were obtained retrospectively from participating institutions, (b) cytological/histological characteristics were not considered in the central review process, and (c) the effects of mogamulizumab on prognosis were not fully evaluated because the number of patients who received mogamulizumab was limited.

In conclusion, the prognoses of patients with acute/lymphoma-type ATL in Japan have improved modestly over the past three decades, but those of patients with chronic/smoldering-type ATL have not improved. Further efforts are warranted to develop better

and safe therapeutic and preventive strategies to improve the prognoses of patients with ATL.

ACKNOWLEDGMENTS

We thank Dr Masanori Shimoyama for the expert opinions on this study. We thank all investigators in hospitals participating in this study. This work was partially supported by Grants-in-Aid from the Ministry of Health, Labour and Welfare of Japan (grant numbers: H23-GanRinsho-Ippan-020 and H26-GanSeisaku-Ippan-006) to MI, UK, TW, and KT and by the Japan Agency for Medical Research and Development (grant numbers: 17ck0106338h0001 and 18ck0106338s0502) to YI, MI, KN, YK, KI, AU, and KT. We also thank Edanz Group (www.edanz.com/ac) for editing a draft of this manuscript.

DISCLOSURE

Kisato Nosaka reports personal fees from Celgene KK; Kenji Ishitsuka reports grants from Kyowa Hakko Kirin Co., Ltd. and personal fees from Celgene KK and Kyowa Hakko Kirin Co., Ltd.; Kenichi Ishizawa reports grants from Novartis, Abbvie, Bayer, and Symbio, and personal fees from Takeda, Celgene KK, Novartis, Ono Pharmaceutical, Chugai Pharma, and Eisai; Takashi Ishida reports grants from Kyowa Hakko Kirin Co., Ltd., Bayer AG, and Celgene KK and personal fees from Kyowa Hakko Kirin Co., Ltd., Celgene KK, and Mundipharma KK; Atae Utsunomiya reports personal fees from Kyowa Hakko Kirin Co., Ltd and Celgene KK; Kensei Tobinai reports grants from Chugai Pharma, Kyowa Hakko Kirin Co., Ltd., Ono Pharmaceutical, Celgene KK, Janssen, Eisai, Mundi Pharma, Takeda, and Abbvie and personal fees from Eisai, Takeda, Mundipharma, HUYA Bioscience International, Kyowa Hakko Kirin Co., Ltd., Celgene KK, Chugai Pharma, Ono Pharmaceutical, Yakult, Daiichi Sankyo, Bristol-Myers Squibb, Meiji Seika Kaisha, Solasia Pharma, Verastem, and Zenyaku Kogyo; Toshiki Watanabe reports grants from Solasia Pharma; Kunihiro Tsukasaki reports scholarship from Chugai Pharma. All the remaining authors have declared no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Imaizumi Y, Iwanaga M, Nosaka K, et al; for collaborative Investigators. Prognosis of patients with adult T-cell leukemia/lymphoma in Japan: A nationwide hospital-based study. *Cancer Sci* 2020;111:4567-4580. <https://doi.org/10.1111/cas.14658>

APPENDIX 1

Collaborative Investigators in participating hospitals

Akifumi Takaori, Masakatsu Hishizawa (Kyoto University); Akira Kitanaka (Miyazaki University); Akiyoshi Takami (Aichi Medical University); Asahi Ito, Takashi Ishida (Nagoya City University); Atae Utsunomiya, Kentaro Yonekura (Imamura General Hospital); Atsuko Mugitani (Fuchu Hospital); Chiaki Kato (Meitetsu Hospital); Daisuke Ogawa (Nagasaki Prefecture Shimabara Hospital); Daisuke Tsuruta (Osaka City University); Eiichi Ohtsuka, Yoshio Saburi (Oita Prefectural Hospital); Eizaburo Sueoka (Saga University); Fujii Kazuyasu, Makoto Yoshimitsu (Kagoshima University); Fujio Matsubara (Shin-Kokura Hospital); Fumi Miyagawa (Nara Medical University); Fumihiko Nakamura, Makoto Sugaya (The university of Tokyo); Hajime Kobayashi (Obihiro Kosei Hospital); Hideho Heizan (Hamanomachi Hospital); Hiroe Fuse (Matsudo City General Hospital); Hirohiko Shibayama (Osaka University); Hiroki Yamaguchi (Nippon Medical School); Hiromasa Harada (Yao Tokusuyukai General Hospital); Hiroshi Ishikawa, Shinichiro Yoshida (Nagasaki Medical Center); Hiroshi Iwasaki (Sapporo-Kosei General Hospital); Hiroshi Kawano (Koga General Hospital); Hiroshi Kazama (Tokyo Women's Medical University); Hiroshi Yamasaki (Kumamoto City Hospital); Hiroyuki Kuroda, Michiko Yamada (Steel Memorial Muroran Hospital); Hitoshi Suzushima (Kumamoto Shinto General Hospital); Ilseung Choi, Naokuni Uike (Kyushu Cancer Center); Kaname

Miyashita (Saiseikai Fukuoka General Hospital); Katsuyasu Saigo (Kobe-Kyodo Hospital); Kazuiku Ohshiro (Nanbu Medical Center/Nanbu Child Medical Center); Kazuki Tatsuno, Yoshiki Tokura, Takaaki Ono (Hamamatsu University School of Medicine); Keiji Sugimoto (Juntendo University Urayasu Hospital); Ken Ohmachi (Tokai University); Kenichiro Etoh (Kumamoto General Hospital); Kenji Ishitsuka, Monji Koga (Fukuoka University); Kensuke Narukawa (National Cancer Center Hospital East); Ki-Ryang Koh (Osaka General Hospital of West Japan Railway Company); Kimiharu Uozumi (Kagoshima Medical Center); Kisato Nosaka (Kumamoto University); Koichi Nagai (Niigata Prefectural Central Hospital); Koji Adachi, Toru Motokura (Tottori University); Koji Izutsu (Toranomon Hospital); Koji Kato (Kyushu University); Koji Nagafuji (Kurume University); Masaaki Yuge (Ichinomiya Municipal Hospital); Masaharu Miyahara (Karatsu Red Cross Hospital); Masakazu Higuchi (Kyushu Hospital); Masaki Hayashi (Nakagami Hospital); Masaki Iino (Yamanashi Prefectural Central Hospital); Masanori Makita (Okayama Medical Center); Masao Hagihara (Eiju General Hospital); Masaru Shibano (Sakai City Medical Center); Masato Ito (Daido Hospital); Masato Saito (Nikko Memorial Hospital); Michiaki Koike (Juntendo University Shizuoka Hospital); Michihiro Hidaka (Kumamoto Medical Center); Mitsutoshi Kurosawa (Hokkaido Cancer Center); Motoharu Fukazawa (Funabashi Central Hospital); Motohiro Shindo (Asahikawa Medical University); Motoi Takenaka, Yoshitaka Imaizumi (Nagasaki University); Naoki Kobayashi (Sapporo Hokuyu Hospital); Nobuharu Kosugi (Numazu City Hospital); Nobuhiko Nakamura (Gifu University); Nobuhiko Tominaga (Suita Municipal Hospital); Noriko Fukuhara (Tohoku University); Rika Sakai (Kanagawa Cancer Center); Ryohei Nawata (Shimonoseki Medical Center); Satoshi Iyama (Sapporo Medical University); Satoshi Yamasaki (Kyushu Medical Center); Sawako Nakachi, Takeaki Tomoyose (University of the Ryukyus); Shigeaki Ito (Iwate Medical University); Shigeru Chiba (University of Tsukuba); Shinya Rai (Kinki University); Takahiro Okada (Shimane University); Takahiro Shimano (Rinku General Medical Center); Takashi Inozume (University of Yamanashi); Takayoshi Ito (JA Toride Medical Center); Takayuki Ikezoe (Kochi University); Takeshi Fujimoto (Nagasaki National Hospital); Tatsuro Jo (Japanese Red Cross Nagasaki Genbaku Hospital); Tatsuya Kaji (Okayama University); Tohru Murayama (Hyogo Cancer Center); Tomohiro Myojo (Edogawa Hospital); Toru Takahashi (Tenshi Hospital); Toru Takahashi (Yamaguchi Prefectural Grand Medical Center); Toshiaki Yujiri (Yamaguchi University); Toshiyuki Nakayama (Tsurumi Hospital); Yoko Adachi (Kobe Central Hospital); Yoshiyasu Kato (Kagoshima Prefectural Satsunan Hospital); Yukio Kobayashi (National Cancer Center Hospital); Yuki Yoshi Moriuchi (Sasebo City General Hospital); Yuko Ogata (Nishi-Beppu National Hospital); Yuta Katayama (Hiroshima Red Cross Hospital & Atomic Bomb Survivors Hospital).